IgA Nephropathy: Management Update

By

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Agenda

- Introduction
- Pathogenesis
- Clinical presentation
- Histopathological features
- Management
  - a- KDIGO
  - b- RCT
- Recurrence after renal transplantation
- Conclusions

IgA Nephropathy: Introduction

- It is also known as Berger's disease, Berger's syndrome and IgA nephritis.
- IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide.
- IgA nephropathy is now recognized to progress to ESRD in 20% to 40 % of patients within 20 years from its onset.

IgA Nephropathy: Distribution

Global distribution of patients with IgA nephropathy in some key regions of the world. Prevalence is shown as percentage of biopsy-proven primary glomerulonephritis.

IgA Nephropathy: Pathogenesis

- Infection (gastrointestinal, pulmonary, urinary) can be the inciting agent. All of these infections have in common the activation of mucosal defenses and hence IgA antibody production.

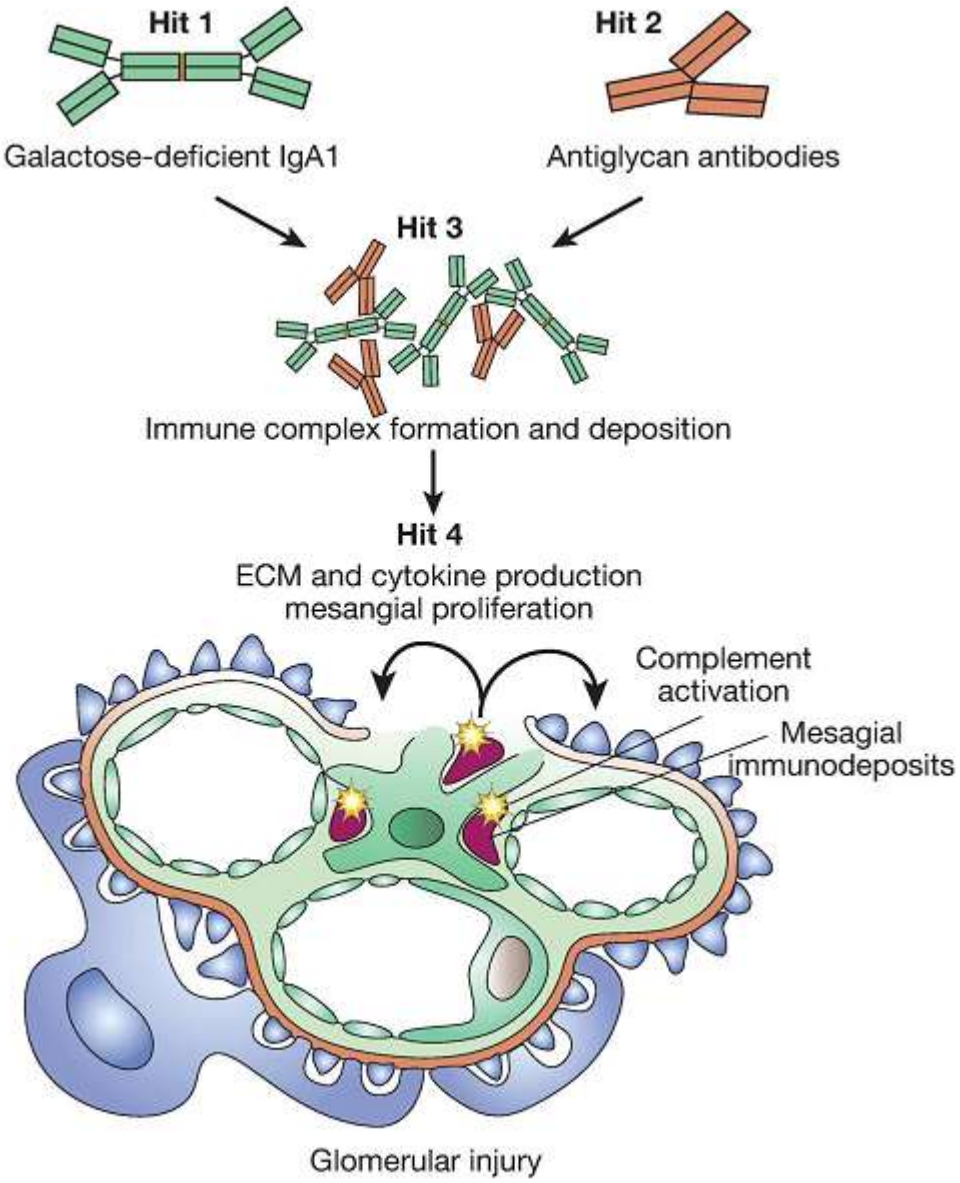
The mucosa–kidney axis in IgA nephropathy

Jürgen Floege[1] and John Feehally[2]

Key points

- Genome-wide association studies in patients with IgA nephropathy (IgAN) have identified risk loci in genes involved in the intestinal mucosal integrity and immune network
- Immune responses to mucosal antigens and immunization studies suggest that the systemic response to mucosal antigens is exaggerated in patients with IgAN
- Patients with IgAN have increased reactivity to dietary proteins associated with subclinical intestinal mucosal inflammation, although in general they do not have overt dietary intolerance
- Very rarely, IgAN is associated with gastrointestinal diseases; whether these diseases indeed share a common pathogenesis or whether gastrointestinal inflammation exacerbates IgAN is uncertain
- Mucosal alterations such as respiratory tract infections could activate the innate immune system, aggravate a pre-existing IgAN and promote disease manifestations such as macrohaematuria, rather than a share a pathogenetic link with IgAN
- Intervention studies targeting the mucosae in IgAN have been inconclusive so far, but new studies are ongoing

The Multi-hit Pathogenesis Model of IgA Nephropathy



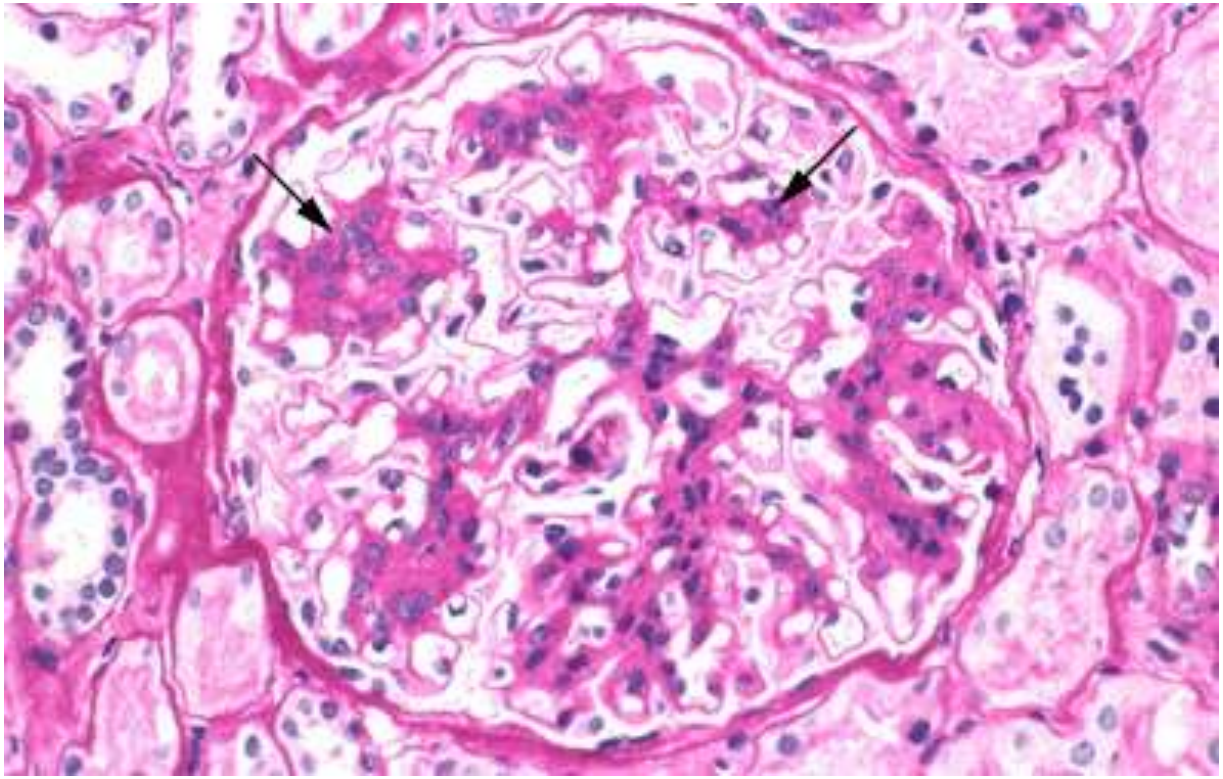
IgA Nephropathy: Clinical presentation

- **Approximately 40 - 50 %** recurrent episodes of macroscopic hematuria, usually following a URI (synpharyngitic hematuria) and episodes usually recur for a few years at most.

- **30 - 40 %** have microscopic hematuria and usually mild proteinuria, and are incidentally detected on a routine examination . These patients, the disease is of uncertain duration. Gross hematuria occur in 20 - 25 % of these patients.

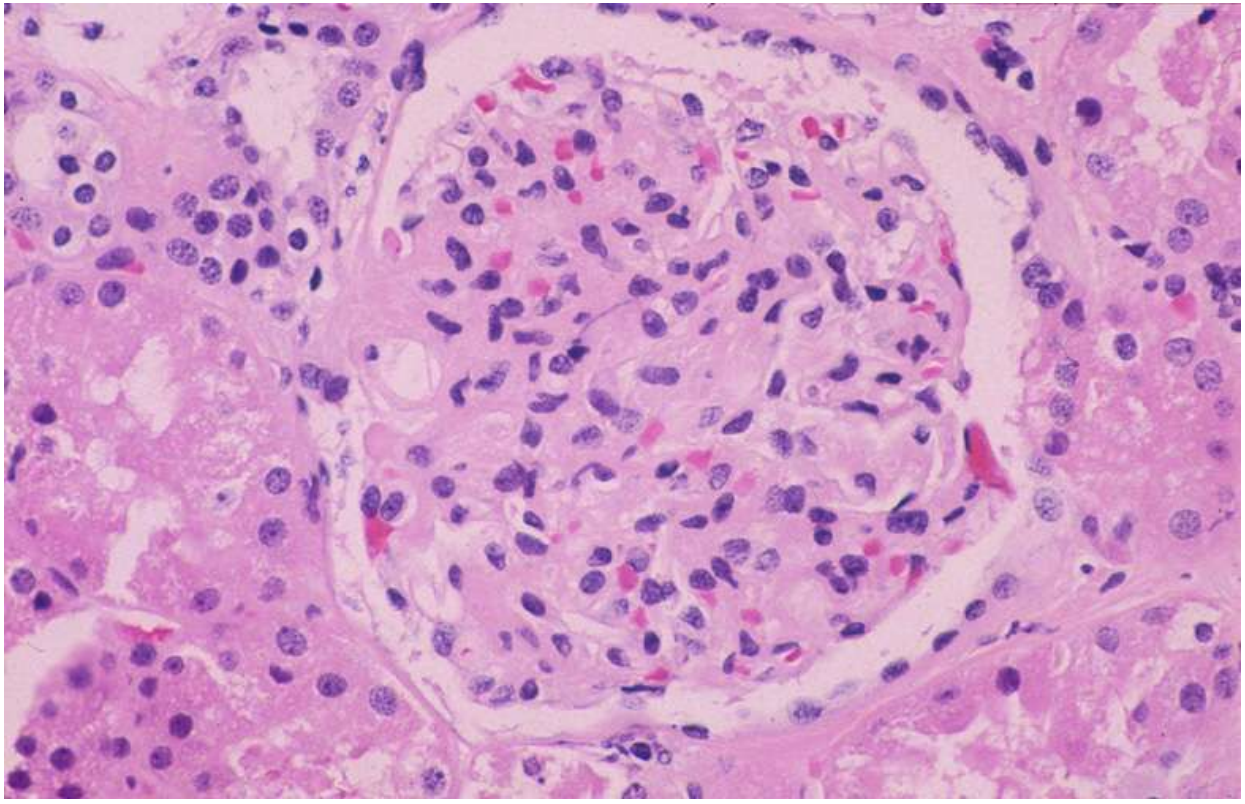
- **Less than 10 %** present with either nephrotic syndrome or acute rapidly progressive glomerulonephritis picture characterized by edema, hypertension, and renal insufficiency as well as hematuria.

IgA Nephropathy: Histopathology



The major finding on light microscopy is mesangial proliferation and matrix expansion (arrows) that can be focal, but more often seen diffusely.

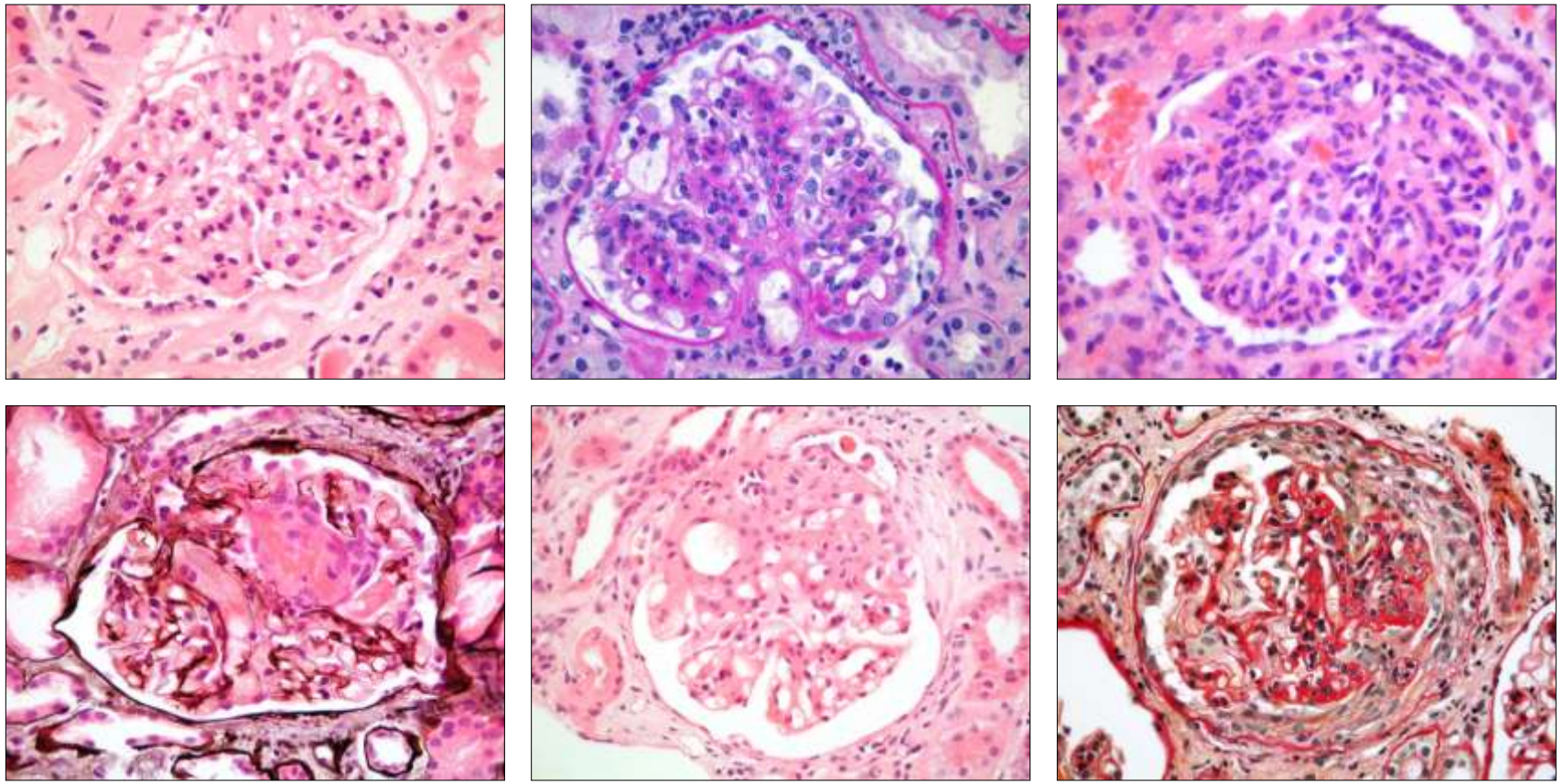
IgA Nephropathy: Histopathology



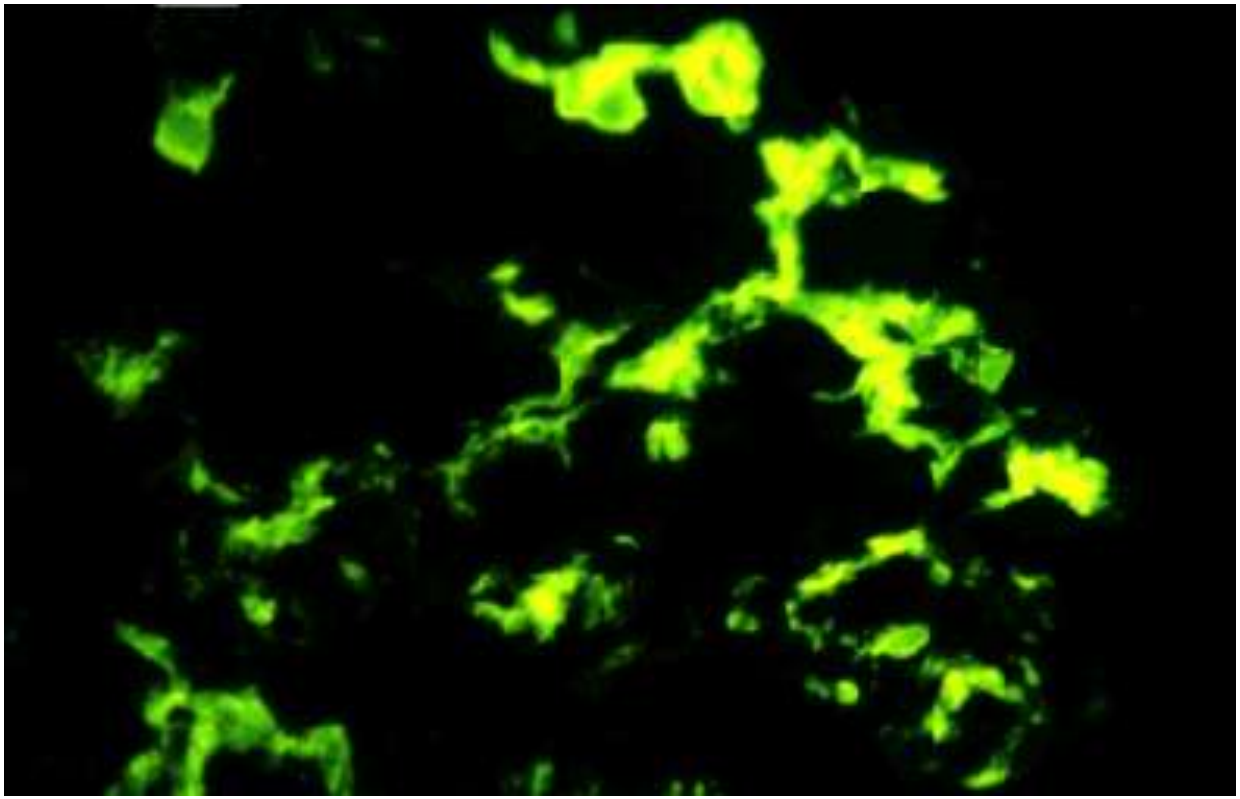
Light microscopy of a glomerulus from a patient with IgAN showing increased mesangial matrix and cellularity.

IgA Nephropathy: Histopathology

IgA nephropathy is heterogeneous

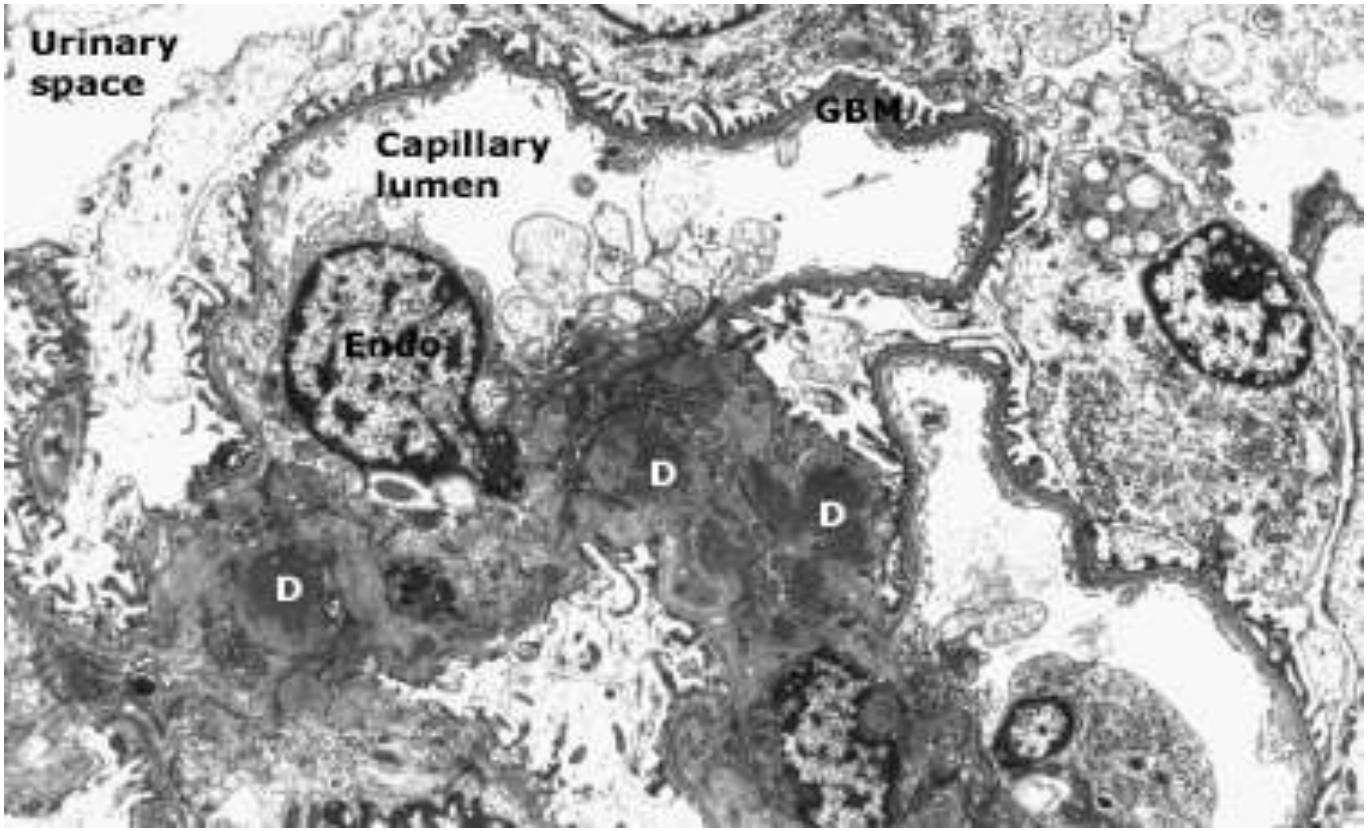


IgA Nephropathy: Histopathology



IF demonstrating large, globular mesangial IgA deposits. Note that the capillary walls are not outlined, since the deposits are primarily limited to the mesangium.

IgA Nephropathy: Histopathology

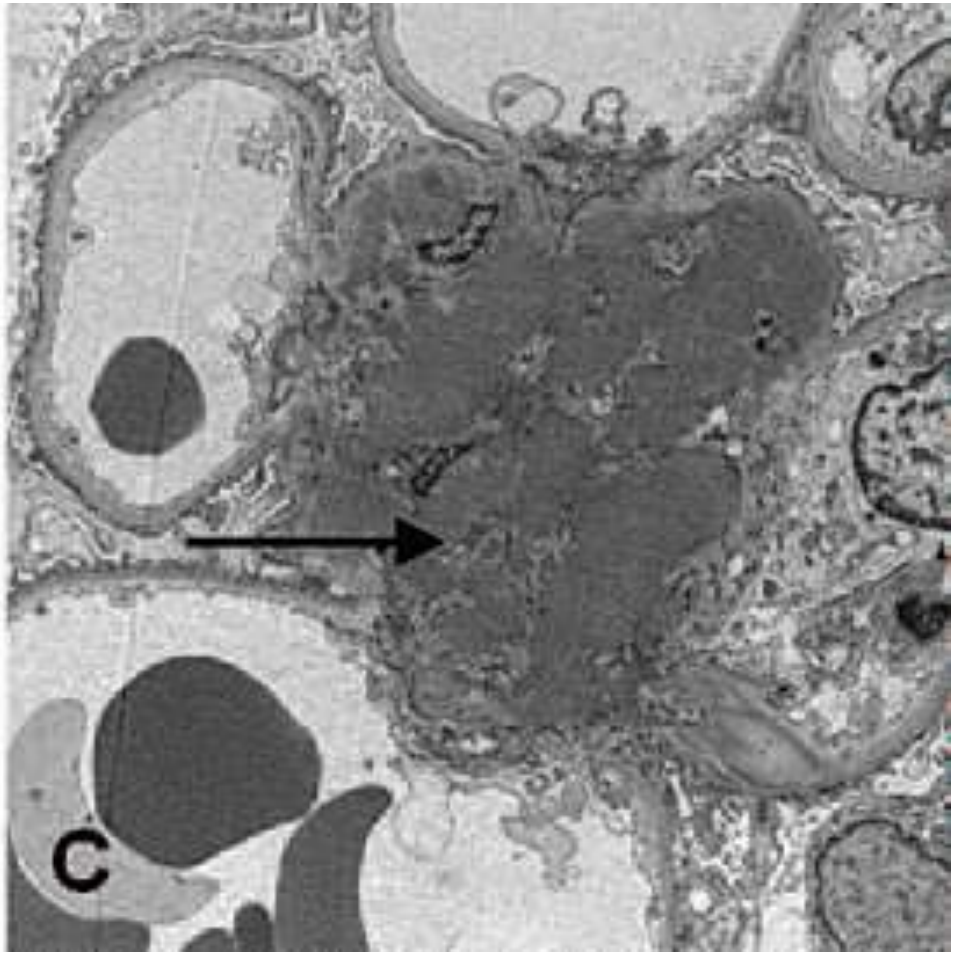


Low power electron micrograph in IgAN.

- The primary finding is electron dense deposits that are limited to the mesangial regions (D).
- The glomerular basement membrane (GBM) is normal and there are no glomerular capillary wall deposits.

IgA Nephropathy: Histopathology

- **Higher power EM:** significant expansion of mesangial matrix and presence of large mesangial dense deposits (arrow).



IgA Nephropathy: Oxford Classification (2009)

An international evidence-based classification of IgA nephropathy: the Oxford Classification

IgA Nephropathy: Oxford Classification (2009)

The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility

A Working Group of the International IgA Nephropathy Network and the Renal Pathology Society: Ian S.D. Roberts[1], H. Terence Cook[2], Stéphan Troyanov[3], Charles E. Alpers[4], Alessandro Amore[5], Jonathan Barratt[6], Francois Berthoux[7], Stephen Bonsib[8], Jan A. Bruijn[9], Daniel C. Cattran[10], Rosanna Coppo[5], Vivette D'Agati[11], Giuseppe D'Amico[12], Steven Emancipator[13], Francesco Emma[14], John Feehally[6], Franco Ferrario[15], Fernando C. Fervenza[16], Sandrine Florquin[17], Agnes Fogo[18], Colin C. Geddes[19], Hermann-Josef Groene[20], Mark Haas[21], Andrew M. Herzenberg[22], Prue A. Hill[23], Ronald J. Hogg[24], Stephen I. Hsu[25], J. Charles Jennette[26], Kensuke Joh[27], Bruce A. Julian[28], Tetsuya Kawamura[29], Fernand M. Lai[30], Lei-Shi Li[31], Philip K.T. Li[32], Zhi-Hong Liu[31], Bruce Mackinnon[19], Sergio Mezzano[33], F. Paolo Schena[34], Yasuhiko Tomino[35], Patrick D. Walker[36], Haiyan Wang[37], Jan J. Weening[38], Nori Yoshikawa[39] and Hong Zhang[37,*]

Pathological classifications in current use for the assessment of glomerular disease have been typically opinion-based and built on the expert assumptions of renal pathologists about lesions historically thought to be relevant to prognosis. Here we develop a unique approach for the pathological classification of a glomerular disease, IgA nephropathy, in which renal pathologists first undertook extensive iterative work to define pathologic variables with acceptable inter-observer reproducibility. Where groups of such features closely correlated, variables were further selected on the basis of least susceptibility to sampling error and ease of scoring in routine practice. This process identified six pathologic variables that could then be used to interrogate prognostic significance independent of the clinical data in IgA nephropathy (described in the accompanying article). These variables were (1) mesangial cellularity score; percentage of glomeruli showing (2) segmental sclerosis, (3) endocapillary hypercellularity, or (4) cellular/fibrocellular crescents; (5) percentage of interstitial fibrosis/tubular atrophy; and finally (6) arteriosclerosis score. Results for interobserver reproducibility of individual pathological features are likely applicable to other glomerulonephritides, but it is not known if the correlations between variables depend on the specific type of glomerular pathobiology. Variables identified in this study withstood rigorous pathology review and statistical testing and we recommend that they become a necessary part of pathology reports for IgA nephropathy. Our methodology, translating a strong evidence-based dataset into a working format, is a model for developing classifications of other types of renal disease.

Kidney International advance online publication, 1 July 2009; doi:10.1038/ki.2009.168

KEYWORDS: glomerulonephritis; IgA nephropathy; Oxford classification; pathology; renal failure

The histological diagnosis of IgA nephropathy is straightforward; it is defined by the presence of IgA-dominant or co-dominant immune deposits within glomeruli, as shown by immunohistochemistry or immunofluorescence. However, biopsies meeting this criterion may show a wide range of histological changes that reflect the clinical diversity of IgA nephropathy. Biopsy appearances may range from virtually normal histology by light microscopy to severe necrotizing, crescentic glomerulonephritis or advanced glomerulosclerosis, and tubular atrophy. There have been numerous clinicopathological studies of IgA nephropathy, the great majority being retrospective, correlating histological changes in diagnostic biopsy with clinical outcome. A number of histological lesions have been reported to be of prognostic value (Table 1).[1–15] The apparently conflicting results of these studies reflect differences in patient cohort, treatment, and clinical outcome measures. In general, studies in which the clinical end point is time to dialysis/renal failure have shown that chronic lesions (tubular atrophy, interstitial fibrosis, and glomerulosclerosis) are the most powerful histological predictors of outcome. This is not surprising, as these lesions reflect an advanced stage of disease; those patients who are biopsied and diagnosed late in the course of their disease will

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*Authors' affiliations are listed in the Acknowledgements.

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The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification

A Working Group of the International IgA Nephropathy Network and the Renal Pathology Society: Daniel C. Cattran[1], Rosanna Coppo[2], H. Terence Cook[3], John Feehally[4], Ian S.D. Roberts[5], Stéphan Troyanov[6], Charles E. Alpers[7], Alessandro Amore[2], Jonathan Barratt[4], Francois Berthoux[8], Stephen Bonsib[9], Jan A. Bruijn[10], Vivette D'Agati[11], Giuseppe D'Amico[12], Steven Emancipator[13], Francesco Emma[14], Franco Ferrario[15], Fernando C. Fervenza[16], Sandrine Florquin[17], Agnes Fogo[18], Colin C. Geddes[19], Hermann-Josef Groene[20], Mark Haas[21], Andrew M. Herzenberg[22], Prue A. Hill[23], Ronald J. Hogg[24], Stephen I. Hsu[25], J. Charles Jennette[26], Kensuke Joh[27], Bruce A. Julian[28], Tetsuya Kawamura[29], Fernand M. Lai[30], Chi Bon Leung[31], Lei-Shi Li[32], Philip K.T. Li[31], Zhi-Hong Liu[32], Bruce Mackinnon[19], Sergio Mezzano[33], F. Paolo Schena[34], Yasuhiko Tomino[35], Patrick D. Walker[36], Haiyan Wang[37], Jan J. Weening[38], Nori Yoshikawa[39] and Hong Zhang[37,*]

IgA nephropathy is the most common glomerular disease worldwide, yet there is no international consensus for its pathological or clinical classification. Here a new classification for IgA nephropathy is presented by an international consensus working group. The goal of this new system was to identify specific pathological features that more accurately predict risk of progression of renal disease in IgA nephropathy, thus enabling both clinicians and pathologists to improve individual patient prognostication. In a retrospective analysis, sequential clinical data were obtained on 265 adults and children with IgA nephropathy who were followed for a median of 5 years. Renal biopsies from all patients were scored by pathologists blinded to the clinical data for pathological variables identified as reproducible by an iterative process. Four of these variables: (1) the mesangial hypercellularity score, (2) segmental glomerulosclerosis, (3) endocapillary hypercellularity, and (4) tubular atrophy/interstitial fibrosis were subsequently shown to have independent value in predicting renal outcome. These specific pathological features withstood rigorous statistical analysis even after taking into account all clinical indicators available at the time of biopsy as well as during follow-up. The features have prognostic significance and we recommended they be taken into account for predicting outcome independent of the clinical features both at the time of presentation and during follow-up. The value of crescents was not addressed due to their low prevalence in the enrolled cohort.

Kidney International advance online publication, 1 July 2009; doi:10.1038/ki.2009.243

KEYWORDS: glomerulonephritis; IgA nephropathy; Oxford classification; pathology; renal failure

IgA nephropathy (IgAN) is the commonest glomerular disease worldwide, yet there is no international consensus for its pathological or clinical classification. Nephrologists use clinical information to identify the risk of developing progressive chronic kidney disease in individual patients with IgAN. There is now extensive evidence that a number of clinical features at presentation predict risk of progressive chronic kidney disease. In published series, these consistently include extent of proteinuria, hypertension, and excretory renal function.[1–5] Recent work also indicates the prognostic importance of reduction in proteinuria during follow-up, allowing continuing refinement of the prognostic information given to an individual patient.[6] Pathologists have developed a number of classifications of IgAN over the last 25 years; some are semiquantitative,[7–10] others are single-grade classifications.[11–15] Each of these classifications has been developed from expert opinion, each has strengths and limitations in predicting prognosis, and none has gained pre-eminence. There is continuing debate whether pathological features seen on renal biopsy contribute additional prognostic information beyond that provided by clinical features.[16]

This lack of consensus on classifications based on pathology has weakened a number of areas of investigation into IgAN. It has contributed to slow progress in developing a prognostic system with the sensitivity and specificity to predict outcome for individual patients. It has reduced the capacity to make international comparisons between

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MEST-Oxford Classification System

- **M**esangial Hypercellularity

  0= <50% 1=>50% glomeruli involved

- **E**ndocapillary proliferation

  0= Absent 1= Present

- **S**egmental glomerulosclerosis

  0= Absent 1=Present

- **T**ubulo-Interstitial Fibrosis

  0= <25% 1= 25-50% 2= >50%

Preliminary Studies Show Good Correlation with Outcome

March, 2016

www.nature.com/scientificreports

OPEN

Selection of urinary sediment miRNAs as specific biomarkers of IgA nephropathy

Received: 12 January 2016
Accepted: 07 March 2016
Published: 22 March 2016

Zhi-Yu Duan, Guang-yan Cai, Ru Bu, Yang Lu, Kai Hou & Xiang-Mei Chen

The miRNAs in urinary sediment are easy to obtain, which provides a new approach to searching

The study showed that the miR-25-3p, miR-144-3p and miR-486-5p in urinary sediment were mainly derived from urinary erythrocytes, which could be non-invasive candidate biomarkers for IgA nephropathy.

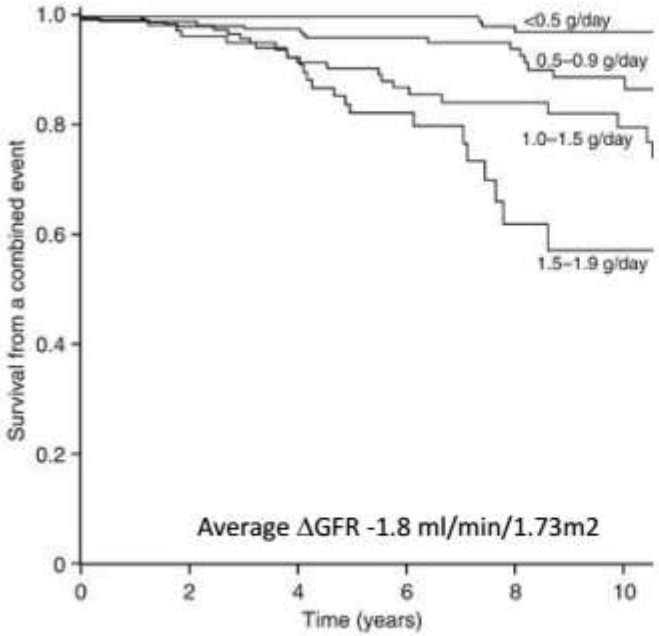
IgA Nephropathy: Outcome Predictors

- Proteinuria
- Histology

IgA Nephropathy: Outcome Predictors

VALIGA data confirm predictive value of time-average proteinuria

2014



Number at risk			
<0.5 g/day	338	198 (59%)	97 (29%)
0.5–0.9 g/day	315	185 (59%)	77 (24%)
1.0–1.5 g/day	167	97 (58%)	46 (28%)
1.5–1.9 g/day	108	68 (63%)	14 (13%)

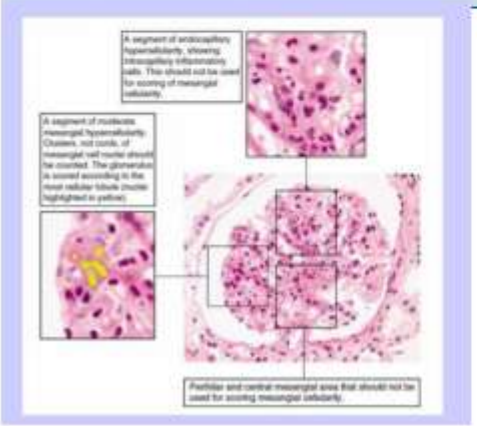
→ Proteinuria > 0.5g/day: risk!

Coppo et al Kidney Int 2014

IgA Nephropathy: Outcome Predictors

The Oxford classification

Mesangial score*	≤ 0.5 (**M0**)	> 0.5 (**M1**)	
Endocapillary hypercellularity	Absent (**E0**)	Present (**E1**)	
Segmental glomerulosclerosis	Absent (**S0**)	Present (**S1**)	
Tubular atrophy/ interstitial fibrosis	≤ 25% (**T0**)	26-50% (**T1**)	>50% (**T2**)



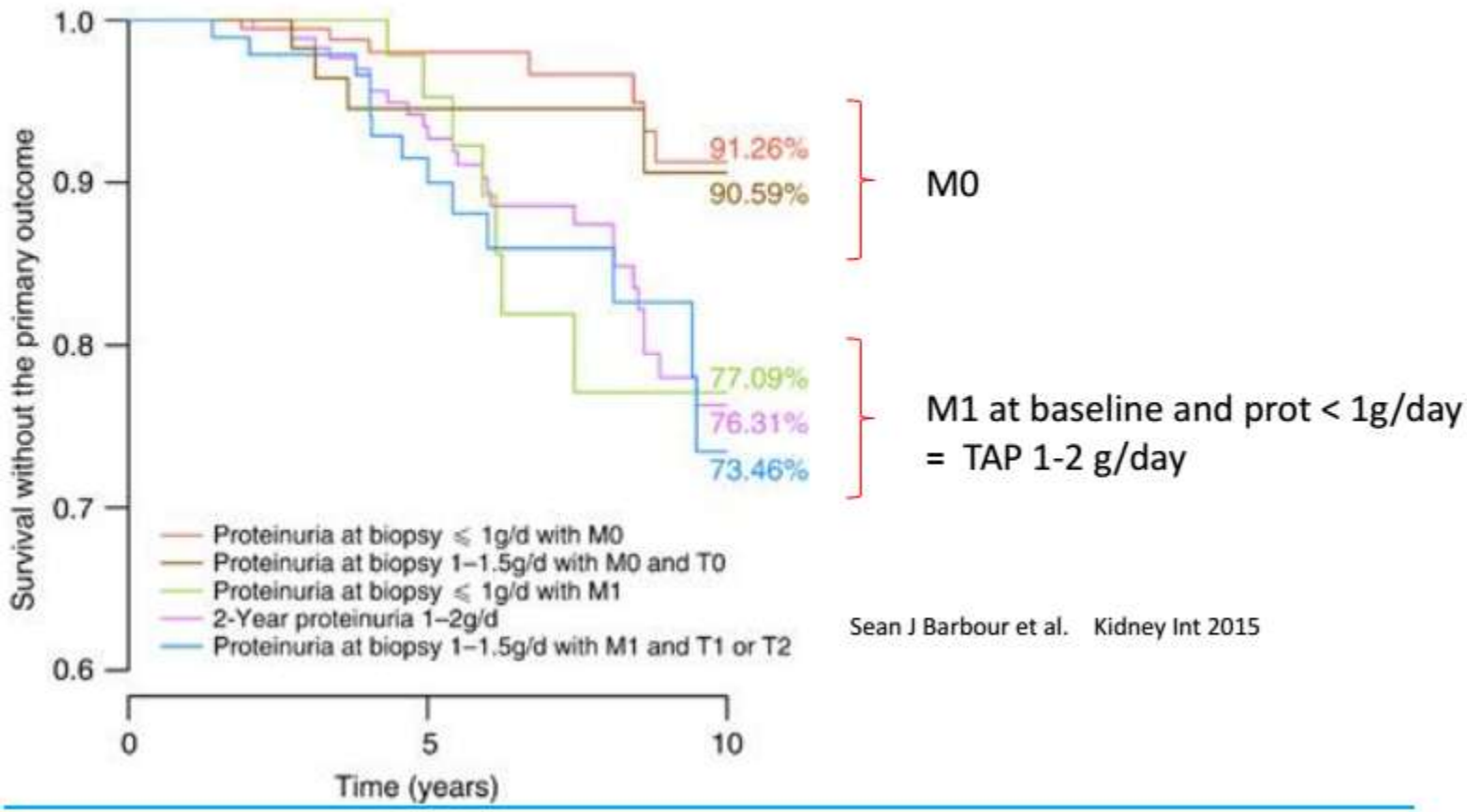
* If >50% of the glomeruli have > 3 cells in a mesangial area this is scored as M1

[1] Roberts, Kidney Int 2009;76(5):546-556; [2] Cattran, Kidney Int 2009;76(5):534-545

IgA Nephropathy: Outcome Predictors

2015

The risk of the primary composite renal outcome



Sean J Barbour et al. Kidney Int 2015

Therapy of IgA Nephropathy

- ACE inhibitors, ARB's, Combinations

- Immunosuppressives:

  Corticosteroids

  Azathioprine + steroids

  Cyclophosphamide + steroids

  Mycophenolate mofetil

  Other (Rituximab, ACTH)

- Fish Oils
- Tonsillectomy

IgA Nephropathy: Management

- **KDIGO Guidelines(2012)**
- **Recent RCT (2015 – 2016)**
  - **Study question**
  - **Important results & conclusions**

KDIGO CLINICAL PRACTICE GUIDELINE FOR GLOMERULONEPHRITIS: IgAN

10.1: Initial evaluation including assessment of risk of progressive kidney disease

10.1.1: Assess all patients with biopsy-proven IgAN for secondary causes of IgAN. (Not Graded)

10.1.2: Assess the risk of progression in all cases by evaluation of proteinuria, blood pressure, and eGFR at the time of diagnosis and during follow-up. (Not Graded)

10.1.3: Pathological features may be used to assess prognosis. (Not Graded)

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10.1.3: Pathological features may be used to assess prognosis. (Not Graded)

10.2: Antiproteinuric and antihypertensive therapy

10.2.1: We recommend long-term ACE-I or ARB treatment **when proteinuria is >1 g/d,** with up-titration of the drug depending on blood pressure. (1B)

10.2.2: We suggest ACE-I or ARB treatment if proteinuria is between 0.5 to 1 g/d. (2D)

10.2.3: We suggest the ACE-I or ARB be titrated upwards as far as tolerated to achieve proteinuria <1 g/d. (2C)

10.2.4: In IgAN, use blood pressure treatment goals of <130/80mmHg in patients with proteinuria < 1 g/d, and <125/75mmHg when initial proteinuria is >1 g/d (see Chapter 2). (Not Graded)

KDIGO CLINICAL PRACTICE GUIDELINE FOR GLOMERULONEPHRITIS: IgAN

10.3: Corticosteroids

10.3.1: We suggest that patients with persistent proteinuria >1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control), and GFR >50 ml/min per 1.73m2, receive a 6-month course of corticosteroid therapy. (2C)

KDIGO CLINICAL PRACTICE GUIDELINE FOR GLOMERULONEPHRITIS: IgAN

10.3: Corticosteroids

10.3.1: **We suggest that patients with persistent proteinuria >1 g/d, despite 3–6 months of optimized supportive care (including ACE-I or ARBs and blood pressure control), and GFR >50 ml/min per 1.73m2, receive a 6-month course of corticosteroid therapy. (2C)**

10.4: Immunosuppressive agents (cyclophosphamide, azathioprine, MMF, cyclosporine)

10.4.1: **We suggest not treating with corticosteroids combined with cyclophosphamide or azathioprine in IgAN patients** (unless there is crescentic IgAN with rapidly deteriorating kidney function; see Recommendation 10.6.3). (2D)

10.4.2: We suggest not using immunosuppressive therapy in patients with GFR <30 ml/min per 1.73m2 unless there is crescentic IgAN with rapidly deteriorating kidney function (see Section 10.6). (2C)

10.4.3: We suggest not using MMF in IgAN. (2C)

KDIGO CLINICAL PRACTICE GUIDELINE FOR GLOMERULONEPHRITIS: IgAN

Box 1 | KDIGO guidelines on the use of corticosteroids in IgAN[1]

Recommendation statement 10.3.1

We suggest that patients with persistent proteinuria >1 g per day, despite 3–6 months of optimized supportive care (including angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers and blood pressure control) and GFR >50 ml/min/1.73 m², receive a 6-month course of corticosteroid therapy (evidence grade 2C).

Recommendation statement 10.4.1

We suggest not treating with corticosteroids combined with cyclophosphamide or azathioprine in IgAN patients, unless there is crescentic IgAN with rapidly deteriorating kidney function (evidence grade 2D).

Recommendation statement 10.4.2

We suggest not using immunosuppressive therapy in patients with GFR <30 ml/min/1.73 m² unless there is crescentic IgAN with rapidly deteriorating kidney function (evidence grade 2C).

***Kidney Int. Suppl*. 2, 139–274 (2012)**

Immunosuppressive therapy in IgA nephropathy: results of recent RCT

Immunosuppressive therapy in IgA nephropathy

- Efficacy of prednisone **(Retrospective analysis of VALIGA data, JASN 2015)**
- Immunosuppressive therapy **(STOP IgA Floege NEJM, 2015)**
- Cyclophosphamide **(Peters et al Neth J Med, 2015)**
- MMF **(small RCT Hogg et al AJKD, 2015)**
- Budosenide **(NEFIGAN, RCT ASN 2015)**
- Rituximab **(on going RCT 2016)**

2015

CLINICAL RESEARCH www.jasn.org

Corticosteroids in IgA Nephropathy: A Retrospective Analysis from the VALIGA Study

Vladimir Tesar,* Stéphan Troyanov,† Shubha Bellur,‡ Jacobien C. Verhave,† H. Terence Cook,§ John Feehally,‖ Ian S.D. Roberts,‡ Daniel Cattran,¶ Rosanna Coppo,** and on behalf of the VALIGA study of the ERA-EDTA Immunonephrology Working Group

The Validation Study of the Oxford Classification of IgAN (VALIGA)

2015

CLINICAL RESEARCH www.jasn.org

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Study Questions

What are the benefits of Steroids to patients with:

- eGFR ≤ 50 ml/min per 1.73 m2
- Other levels of proteinuria
- Different renal pathologic lesions

2015

CLINICAL RESEARCH www.jasn.org

Corticosteroids in IgA Nephropathy: A Retrospective Analysis from the VALIGA Study

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Study design

Multicenter Trial:

- 13 European countries
- 1147 patients

2015

Corticosteroids in IgA Nephropathy: A Retrospective Analysis from the VALIGA Study

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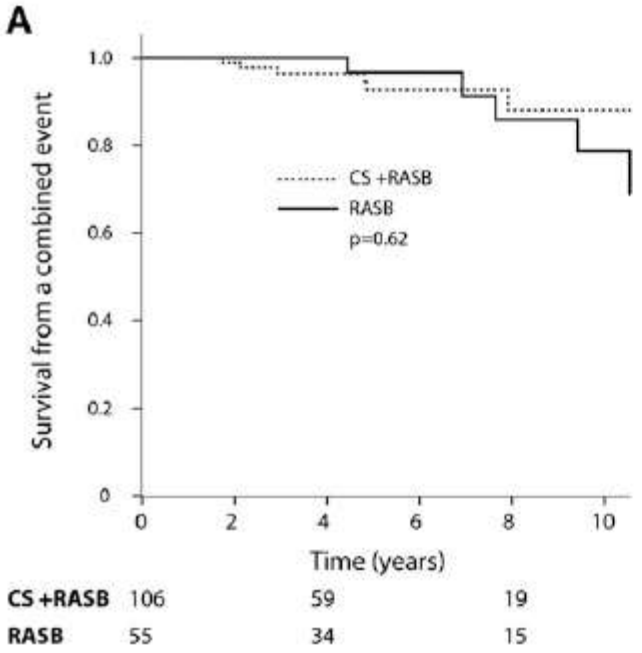
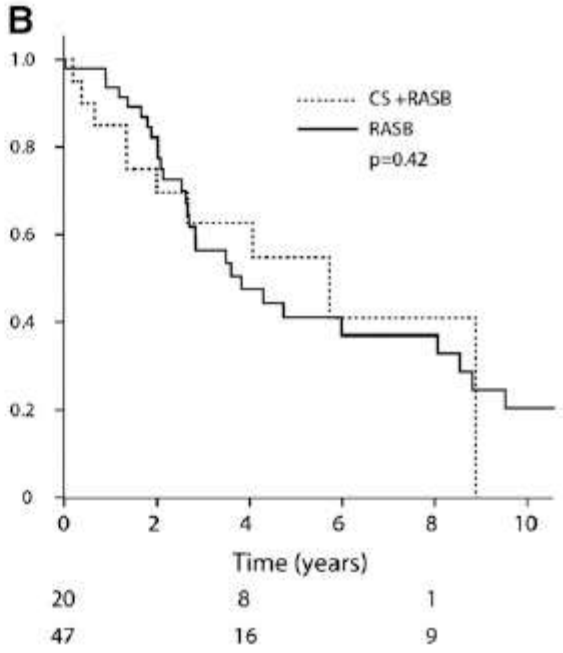
Proteinuria < 1 g



Proteinuria > 1 g

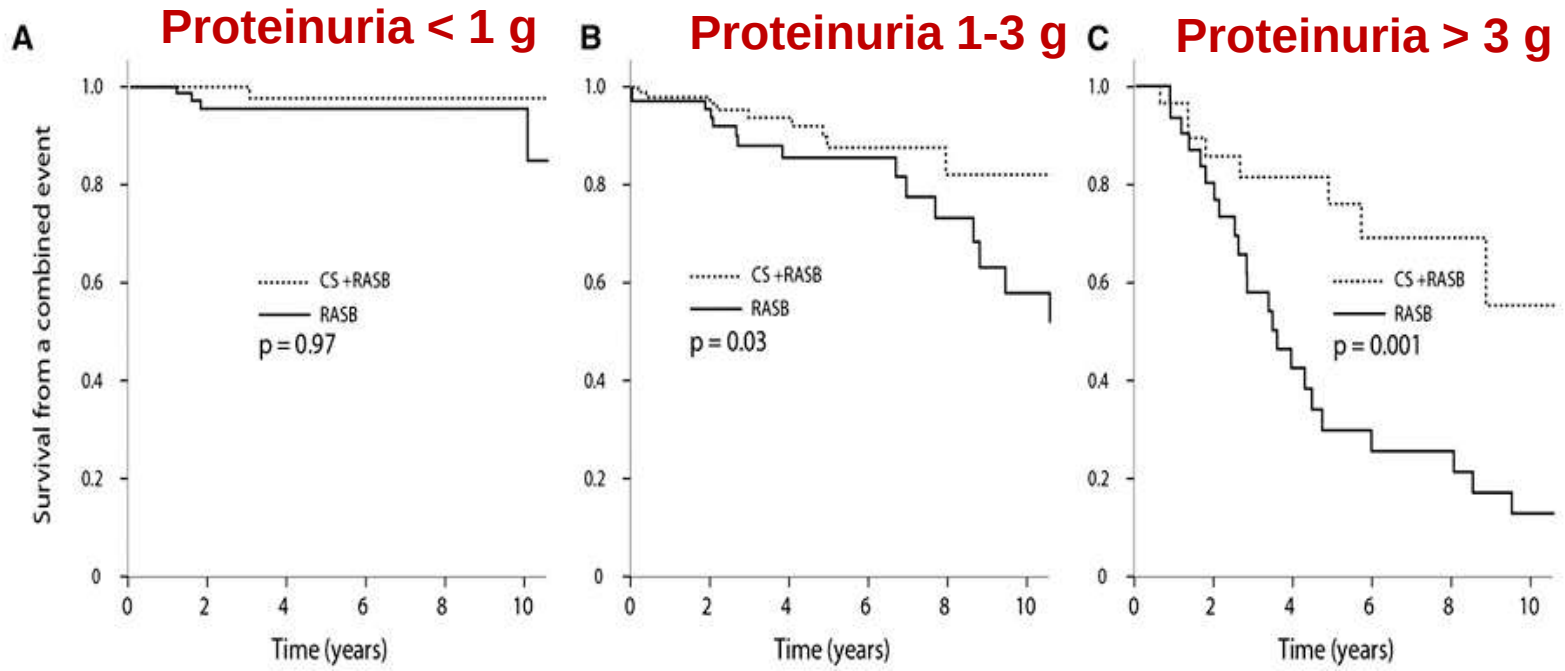


Corticosteroid therapy in IgA nephropathy

Efficacy of prednisone confirmed in retrospective analysis of VALIGA data.

Proteinuria

2015



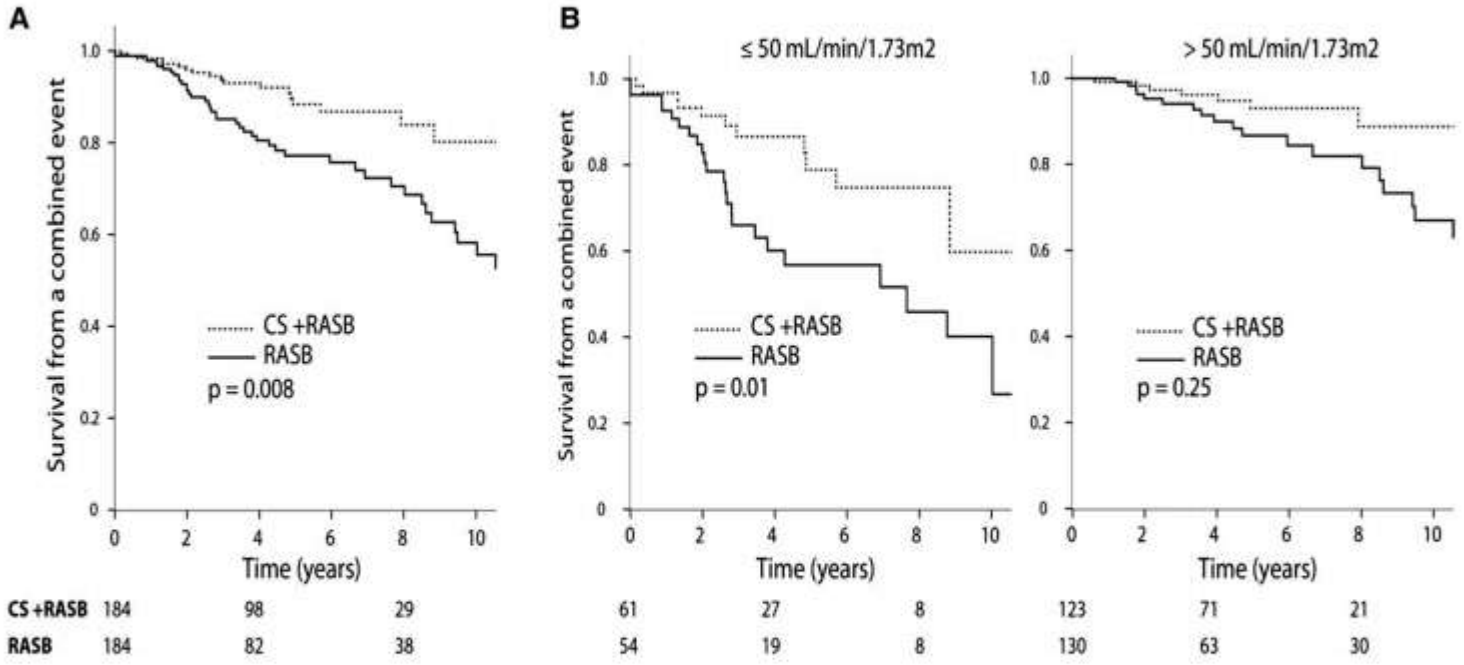
Tesar V et al JASN 2015

Corticosteroid therapy in IgA nephropathy

Efficacy of prednisone confirmed in retrospective analysis of VALIGA data.

GFR

2015



Tesar V et al JASN 2015

Corticosteroid therapy in IgA nephropathy

Efficacy of prednisone confirmed in retrospective analysis of VALIGA data.

MEST-Score

2015

Variable	n	Slope (ml/min per 1.73 m^2/y)	*P* Value	n[a] (with Initial Proteinuria>1 g/d)	Reaching Proteinuria<1 g/d (%)	*P* Value
Pathology findings						
M0						
RASB	129	−2.1±8.0	0.08	60	53	<0.001
CS and RASB	127	−0.6±5.8		78	85	
M1						
RASB	55	−6.1±8.5	0.01	42	57	0.003
CS and RASB	57	−1.8±9.7		48	80	
E0						
RASB	167	−3.2±8.5	0.01	90	52	<0.001
CS and RASB	165	−1.0±7.1		112	84	
E1						
RASB	17	−4.7±5.5	0.10	12	67	0.28
CS and RASB	19	−0.6±8.5		14	86	
S0						
RASB	45	−2.3±7.3	0.21	14	63	0.14
CS and RASB	44	−0.6±4.7		24	83	
S1						
RASB	139	−3.7±8.6	0.009	86	52	<0.001
CS and RASB	140	−1.1±7.9		102	84	
T0						
RASB	135	−2.7±9.0	0.09	62	60	<0.001
CS and RASB	132	−1.0±7.4		85	88	
T1						
RASB	49	−5.0±5.9	0.002	40	45	0.004
CS and RASB	52	−0.9±6.9		41	76	

2015

CLINICAL RESEARCH www.jasn.org

Corticosteroids in IgA Nephropathy: A Retrospective Analysis from the VALIGA Study

Vladimir Tesar,* Stéphan Troyanov,† Shubha Bellur,‡ Jacobien C. Verhave,† H. Terence Cook,§ John Feehally,‖ Ian S.D. Roberts,‡ Daniel Cattran,¶ Rosanna Coppo,** and on behalf of the VALIGA study of the ERA-EDTA Immunonephrology Working Group

Conclusions

Steroids added benefits to RASB to patients with:

- eGFR ≤ 50 ml/min per 1.73 m2
- Proteinuria > 1gm
- Different renal pathologic lesions

2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Supportive Care plus Immunosuppression in IgA Nephropathy

Thomas Rauen, M.D., Frank Eitner, M.D., Christina Fitzner, M.Sc., Claudia Sommerer, M.D., Martin Zeier, M.D., Britta Otte, M.D., Ulf Panzer, M.D., Harm Peters, M.D., Urs Benck, M.D., Peter R. Mertens, M.D., Uwe Kuhlmann, M.D., Oliver Witzke, M.D., Oliver Gross, M.D., Volker Vielhauer, M.D., Johannes F.E. Mann, M.D., Ralf-Dieter Hilgers, Ph.D., and Jürgen Floege, M.D., for the STOP-IgAN Investigators*

STOP-IgAN ClinicalTrial

multicenter, open-label, randomized, controlled trial

2015

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Study Question

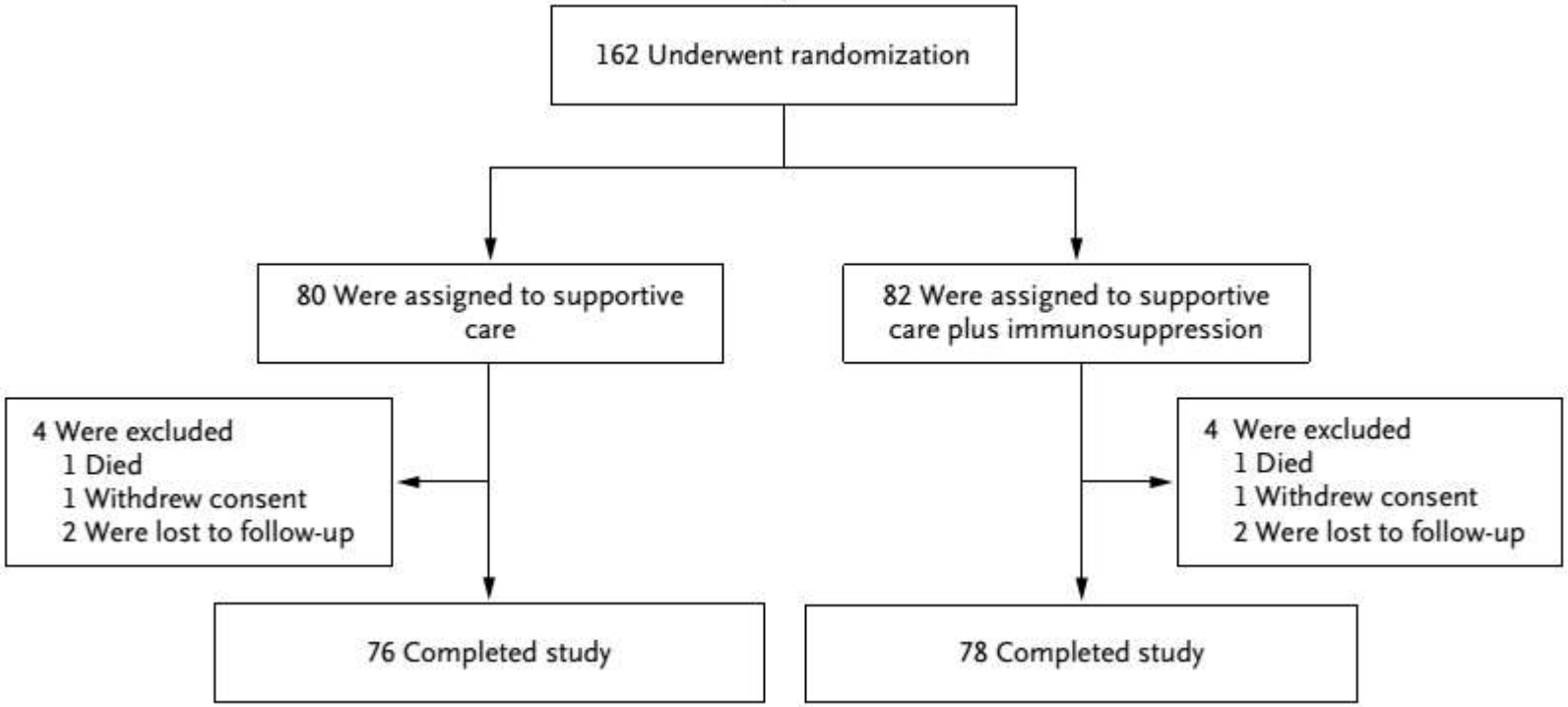
Does immunosuppressive therapy plus comprehensive supportive care would be superior to supportive care alone in patients with IgA nephropathy?

2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Supportive Care plus Immunosuppression in IgA Nephropathy



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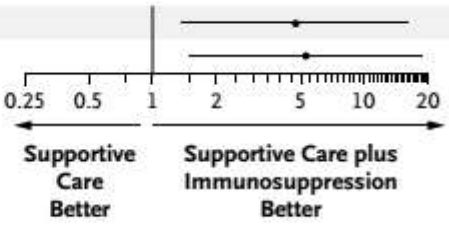
ORIGINAL ARTICLE

Intensive Supportive Care plus Immunosuppression in IgA Nephropathy

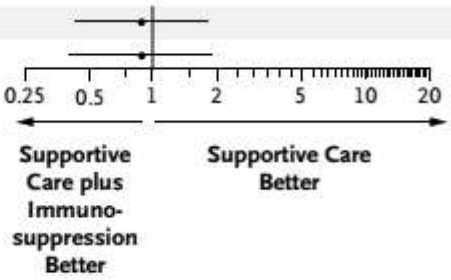
A In Full Clinical Remission

Subgroup	Supportive Care	Supportive Care plus Immunosuppression	Odds Ratio (95% CI)	P Value
	no. of events/total no.			
Full-analysis set	4/80	14/82	4.82 (1.43–16.30)	0.01
Available-case analysis	4/72	14/71	5.38 (1.55–18.66)	0.008



B eGFR Decrease ≥15 ml/min/1.73 m²

Subgroup	Supportive Care	Supportive Care plus Immunosuppression	Odds Ratio (95% CI)	P Value
	no. of events/total no.			
Full-analysis set	22/80	21/82	0.89 (0.44–1.81)	0.75
Available-case analysis	18/76	17/78	0.89 (0.41–1.90)	0.76



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ORIGINAL ARTICLE

Intensive Supportive Care plus Immunosuppression in IgA Nephropathy

Table 3. Adverse Events during the Trial.

Variable	Supportive Care (N=80)	Supportive Care plus Immunosuppression (N=82)	P Value
Patients with ≥1 serious adverse event — no.	21	29	0.24
Total no. of serious adverse events	29	33	0.18
Total no. of events of infection	111	174	0.07
Total no. of serious adverse events of infection	3	8	0.21
Diverticulitis or appendicitis	1	3	0.62
Pneumonia or respiratory tract infection	1	3	0.62
Viral exanthema	1	1	1.00
Knee empyema	0	1	1.00
Death — no.*	1	1	1.00
Additional adverse events of interest — no. of patients			
≥1 incidence of increase in liver-enzyme level (i.e., alanine aminotransferase >50 IU/ml)	12	13	1.00
≥1 incidence of observed leukopenia (i.e., leukocyte count <4000/μl)	3	2	1.00
Malignant neoplasm	0	2	0.50
Impaired glucose tolerance or diabetes mellitus	1	9	0.02
Gastrointestinal bleeding	0	0	Not determined
Fracture	0	1	1.00
Osteonecrosis — no. of patients	0	0	Not determined
Weight gain (≥5 kg within the first year)	5	14	0.049

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CONCLUSIONS

The addition of immunosuppressive therapy to intensive supportive care in patients with high-risk IgA nephropathy did not significantly improve the outcome, and during the 3-year study phase, more adverse effects were observed among the patients who received immunosuppressive therapy, with no change in the rate of decrease in the eGFR. (Funded by the German Federal Ministry of Education and Research; STOP-IgAN ClinicalTrials.gov number, NCT00554502.)

GLOMERULAR DISEASE

Addition of immunosuppression to supportive care does not STOP-IgAN

> The STOP-IgAN study certainly raises a major question mark for immuno-suppression

Nature Reviews Nephrology | Published online 21 Dec 2015

GLOMERULAR DISEASE

Immunosuppressant-induced reduction of proteinuria in IgAN

Jürgen Floege and Thomas Rauen

> “corticosteroid treatment [of IgAN] comes at the price of serious adverse events”

www.nature.com/nrneph

JULY 2016 | VOLUME 12

JULY 2015, VOL. 73, NO 6

The Netherlands Journal of Medicine

ORIGINAL ARTICLE

Immunosuppressive therapy in patients with IgA nephropathy

H.P.E. Peters[1]*, J.A.J. van den Brand[2], S.P. Berger[3], J.F.M. Wetzels[2]

[1]Department of Internal Medicine, Isala Clinics, Zwolle, the Netherlands, [2]Department of Nephrology, Radboud University Medical Centre, Nijmegen, the Netherlands, [3]Department of Nephrology, Leiden University Medical Centre, Leiden, the Netherlands, *corresponding author: tel.: +31(0)38-4245544, fax: +31(0)38-4243001, email: hi.peters@isala.nl

Cyclophosphamide in IgA nephropathy

Cyclophosphamide attenuates progression in proteinuric IgAN

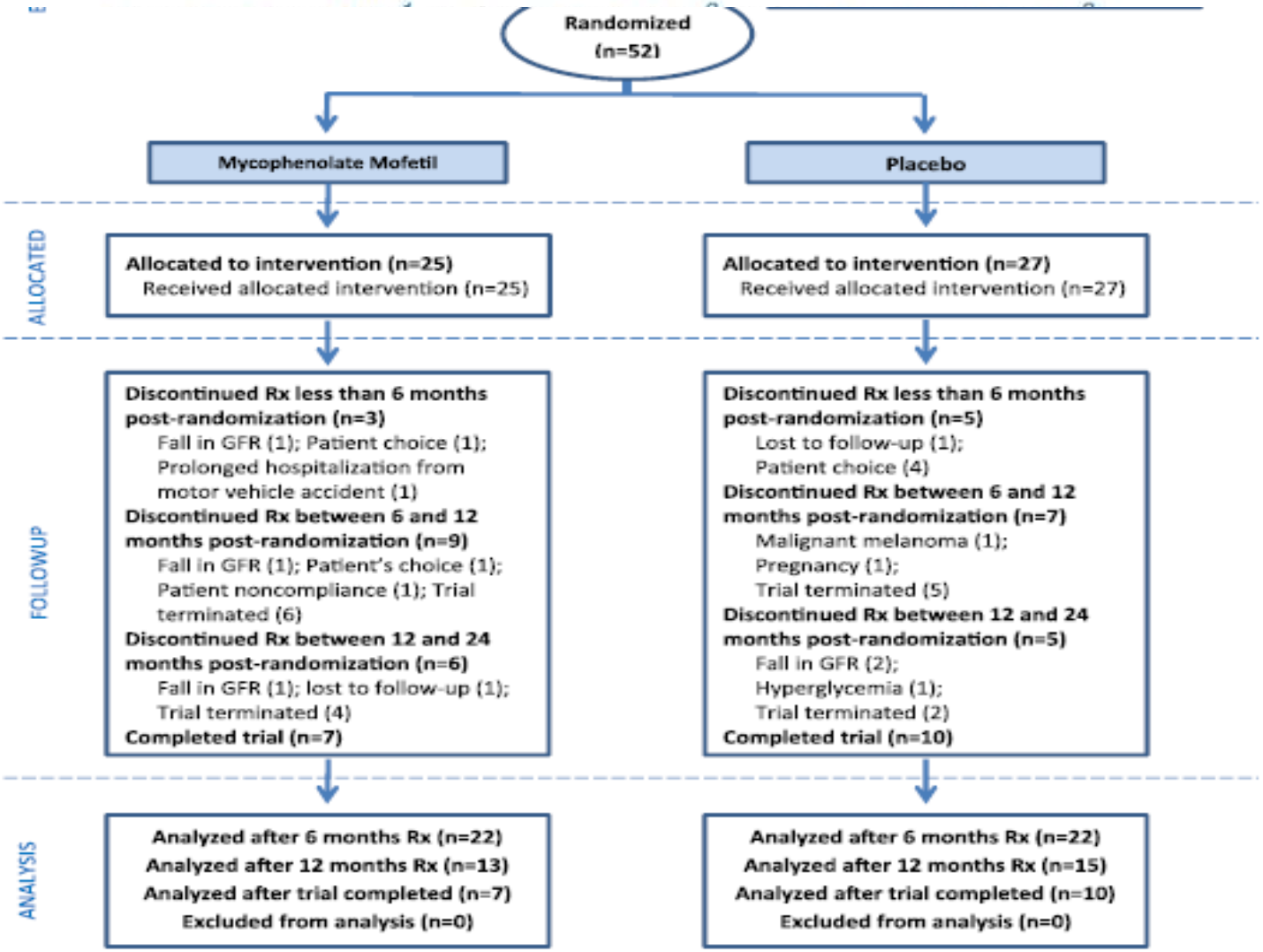
2015

	Progression (n=10)	No progression (n=9)	P value
Sex (M/F)	7/3	7/2	0.70
Age (years)	44±14	40±7	0.42
Serum creatinine (µmol/L)	224 [96-490]	183 [120-381]	0.23
eGFR (ml/min/1.73m²)	26 [12-65]	36 [17-46]	0.21
Proteinuria (g/10mmol creatinine)	4.1 [0.7-18.2]	2.2 [0.6-6.8]	0.31
MAP (mmHg)	104±11	104±10	0.96
Duration of treatment (months)#	16 [3-81]	22 [3-63]	0.50
Follow-up (months)	26 [6-81]	82 [28-133]	0.01
Reduction in proteinuria of ≥50% within 6 months	3	8	0.01
Persistent protein-creatinine ratio <1g/10 mmol	3	8	0.01

Peters H et al Neth J Med 2015

AJKD
Am J Kidney Dis. 66(5):783-791. © 2015
Original Investigation

Randomized Controlled Trial of Mycophenolate Mofetil in Children, Adolescents, and Adults With IgA Nephropathy



AJKD Am J Kidney Dis. 66(5):783-791. © 2015

Original Investigation

Randomized Controlled Trial of Mycophenolate Mofetil in Children, Adolescents, and Adults With IgA Nephropathy

Ronald J. Hogg, MD,[1] R. Curtis Bay, PhD,[2] J. Charles Jennette, MD,[3] Richard Sibley, MD,[4] Sumit Kumar, MD,[5] Fernando C. Fervenza, MD,[6] Gerald Appel, MD,[7] Daniel Cattran, MD,[8] Danny Fischer, MD,[9] R. Morrison Hurley, MD,[10] Jorge Cerda, MD,[11] Brad Carter, MD,[12] Beverly Jung, MD,[13] German Hernandez, MD,[14] Debbie Gipson, MD,[15] and Robert J. Wyatt, MD[16]

Conclusions: MMF did not reduce proteinuria significantly in patients with IgAN who had persistent proteinuria after lisinopril/losartan plus Omacor.

Rituximab in IgA nephropathy

Rituximab in Progressive IgA Nephropathy

Status: Completed

Study Phase: Phase 4

Start Date: February 2009 | **Completion Date:** September 2015

Condition(s): IgA Nephropathy

Full Title of Study

A Multicenter, Randomized, Prospective, Open-Label Trial of Rituximab in the Treatment of Progressive IgA Nephropathy

ClinicalTrials.gov processed this data on July 26, 2016

Nephrol Dial Transplant (2011) 26: 3237–3242
doi: 10.1093/ndt/gfr052
Advance Access publication 4 March 2011

New treatment for IgA nephropathy: enteric budesonide targeted to the ileocecal region ameliorates proteinuria

Hilde Kloster Smerud[1], Peter Bárány[2], Karin Lindström[2], Anders Fernström[3], Anna Sandell[3], Peter Påhlsson[4] and Bengt Fellström[1]

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Locally acting glucocorticoid budesonide (Nefecon) was designed using a modification of the TARGIT starch capsule technology to release the active compound in the distal part of the ileum and the proximal part of the colon where the Peyer’s patches are located.

Nephrol Dial Transplant (2011) 26: 3237–3242
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Hypothesis

targeted release of budesonide will exert its effects by local immunosuppression and suppression of immune complex formation and that the local administration will minimize the systemic side effects seen with oral corticosteroids.

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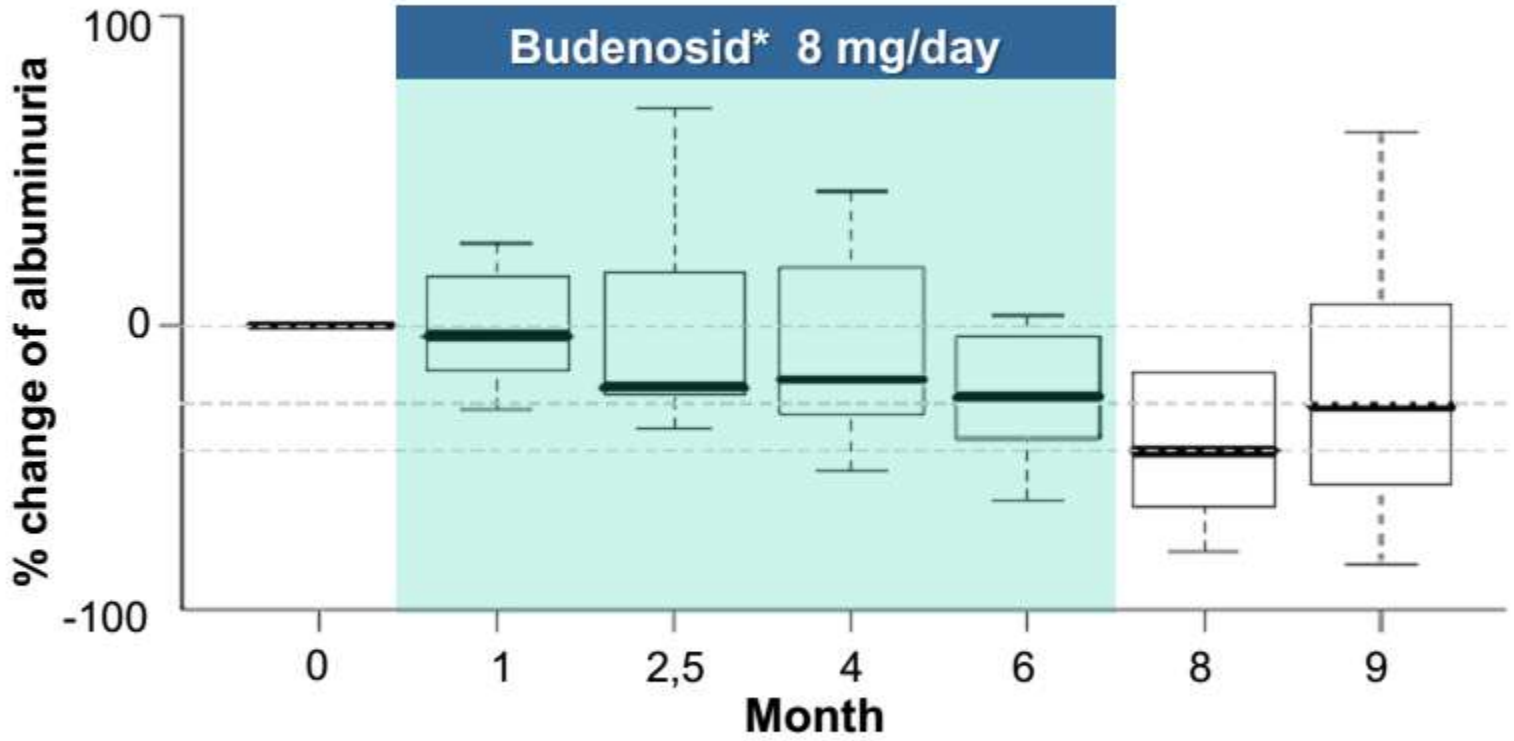
- Budesonide 8 mg/day
- 16 patients with IgAN for 6 months
- 3-month follow-up period.
- Monitoring:
  - 24-h urine albumin excretion
  - serum creatinine
  - eGFR

Budenosid in IgA nephropathy

IgAN: topical immunosuppression



* Special release formulation with release in the ileocecal region

Kloster Smerud H et al, NDT 2011

Budenosid in IgA nephropathy

Results of the NEFIGAN trial:

RCT (ASN 2015)

Treatment 9 months
Baseline: eGFR 78 ml/min/1.73m2
Baseline: proteinuria 1.2 g/day

Results:
significant, 25% reduction of proteinuria
Significant attenuation of eGFR slope:

Maar: ΔeGFR in control group: 7 ml/min/1.73m^2

Nephrol Dial Transplant (2011) 26: 3237–3242
doi: 10.1093/ndt/gfr052
Advance Access publication 4 March 2011

New treatment for IgA nephropathy: enteric budesonide targeted to the ileocecal region ameliorates proteinuria

Hilde Kloster Smerud[1], Peter Bárány[2], Karin Lindström[2], Anders Fernström[3], Anna Sandell[3], Peter Påhlsson[4] and Bengt Fellström[1]

Conclusions. In the present pilot study, enteric budesonide targeted to the ileocecal region had a significant effect on urine albumin excretion, accompanied by a minor reduction of serum creatinine and a modest increase of eGFR

Enteric budesonide may represent a new treatment of IgAN warranting further investigation.

Recurrent IgA Nephropathy after kidney transplantation

Review

Transplantation ■ Month 2016 ■

Recurrent IgA Nephropathy After Kidney Transplantation

Melanie L. Wyld[1,2] and Steven J. Chadban[1,2,3]

- IgA recurs in up to 60% of patient's grafts
- IgA recurrence leads to graft failure in a growing portion of patients as time from transplant lengthens.

23 reports (1994 – 2014)

TABLE 1.

Epidemiology of recurrence after transplant

Author (year)	Follow-up, y	IgA population (% biopsied)	Biopsy indication	Histological recurrence rate		Graft loss from recurrence (% of total)
				IgA population (total)	IgA population (biopsied)	
Registry studies						
Briganti (2002)	≥10	532 (NA)	NA	—	—	10%[a]
Clayton (2011)	Median 7 (IQR, 3-11)	1521 (NA)	NA	—	—	4%[a]
McDonald (2006)	NA	1386 (NA)	NA	8%	—	2%[a]
Andresdottir (2005)	NA (range, 2-14)	1207 (NA)	NA	—	—	2%[a]
Multicenter cohort studies						
Han (2010)	Median, 6 (range, 4-9)	221 (NA)	Clinical	31%[a]	—	—
Odum (1994)	NA (range, 0-15)	51 (57%)	Mixed protocol and clinical biopsy	33%	59%	2%
Single-center cohort studies						
Berthoux (2008)	Mean, 8 ± 5	116 (51%)	Clinical	36%[a]	56%	6%
Freese (1999)	Median, 6 (range, 1-13)	104 (34%)	Clinical	13%	37%	6%
Courtney (2006)	Median, 5 (range, 2-22)	75 (33%)	Clinical	17%	52%	9%
Ortiz (2012)	Median, 5 (range, 1-10)	65 (100%)	Protocol (75% of biopsies taken between 6 and 12 mo)	32%	32%	3%
Ohmacht (1997)	5 ± 1	61 (54%)	Clinical	33%	61%	16%
Wang (2001)	Mean, 4; median, 5 (range, 2-13)	48 (38%)	Clinical	29%	78%	10%
Sato (2014)	Mean, 2 ± 2 (range, 1-7)	78 (100%)	Protocol (0 hr, 1, 12 and 24 mo) + clinical	15%	15%	—
Moriyama (2005)	NA	49 (55%)	Clinical	27%	48%	—
Berger (1988)	NA	32 (100%)	Protocol (6 mo, 2, 4 and 10 y) (+clinical) Case control	53%	53%	0%
Moroni (2013)	Median, 9 (range, 5-14)	190 (59%)	Clinical	22%	37%	6%
Choy (2003)	Mean, 8 ± 1	75 (47%)	Clinical	19%	40%	4%
Ponticelli (2001)	Mean, 6 ± 4; median, 5 (range, 1-10)	106 (54%)	Mixed biopsy reason. (47 clinical biopsies, 10 protocol biopsies)	35%	65%	4%
Andresdottir (2001)	Mean, 6 ± 5	79 (54%)	Clinical	22%	53%	6%
Kim (2001)	Mean, 5 (range, 0-14)	90 (48%)	Clinical	21%	44%[a]	2%
Bumgardner (1998)	Mean, 5 ± 3	61	Clinical	30%	—	10%

Recurrent IgA Nephropathy: Management options

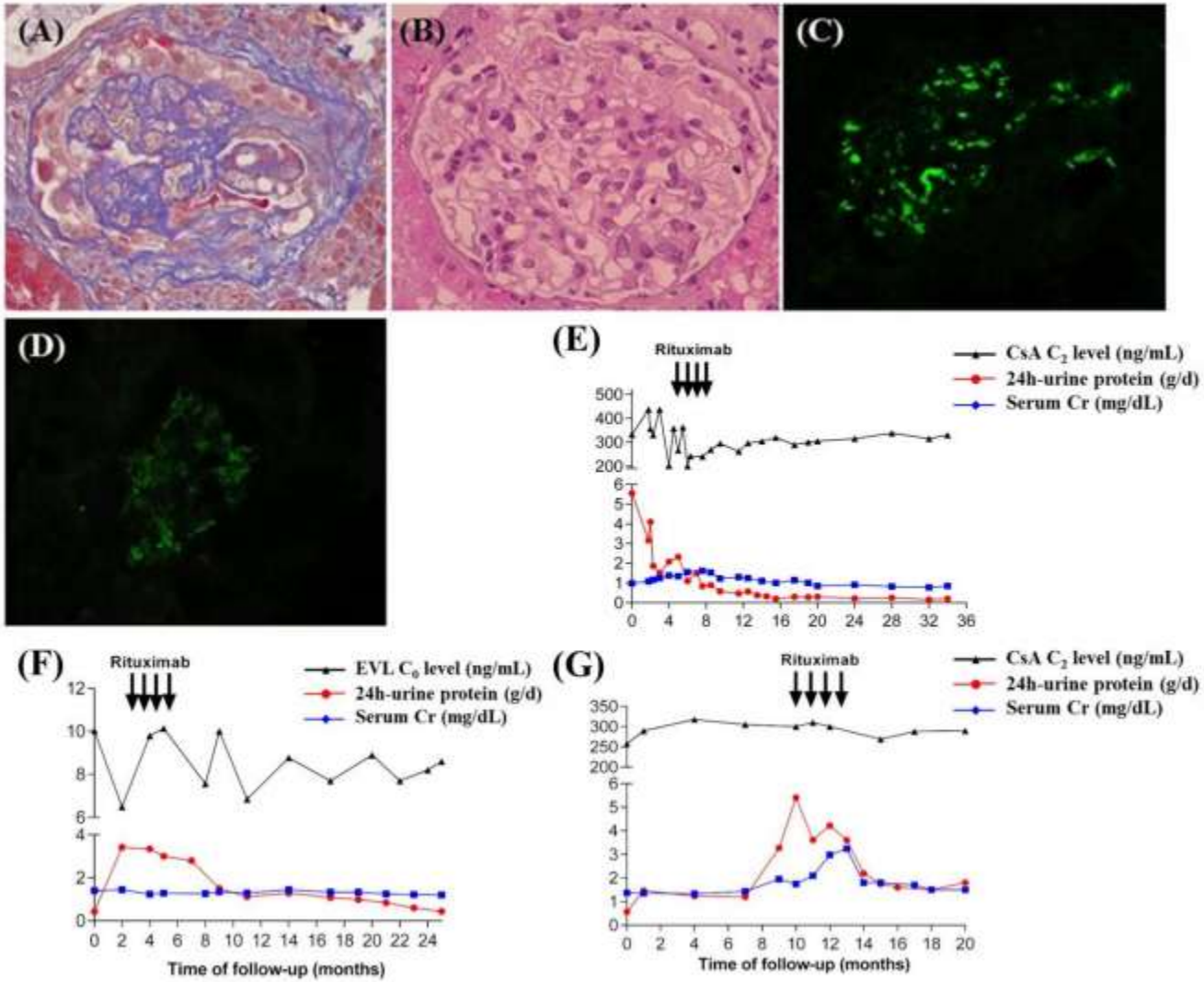
Prevention

- Avoid steroid avoidance protocols
- Induction therapy (ATG)
- Combination (TAC & MMF)

Treatment

- There are no proven, specific therapies for recurrent IgAN.
- Treatment aims to reduce proteinuria and optimize blood pressure by ACEI or ARBS.

Rituximab for Recurrent IgA Nephropathy in Kidney Transplantation: A Report of 3 Cases and Proposed Mechanisms



Transplantation, 2016 (In press)

IgA Nephropathy: Conclusion

1. Accurate prediction of prognosis at baseline: impossible
    - Proteinuria
    - MEST score may be valuable in selected cases
2. Time averaged proteinuria during follow-up is the best parameter
3. Treatment:
    - Steroids: useful, after assessment of proteinuria and GFR
    - Cyclophosphamide: in selected patients, with persistent severe, proteinuria or renal insufficiency; evaluation after max 6 months
    - MMF: not effective
    - Rituximab: waiting for results of ongoing RCT
    - Budosenide: interesting, needs further proof

September 15th - 17th, 2016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